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HORMONAL MEDICATION FOR TRANSSEXUALS

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Abstract

Successful transformation from one sex role to the other is greatly dependent on development of adequate secondary sexual characteristics associated with the desired sex role. For this reason hormone therapy is one of the first reassignment procedures sought by transsexual persons. Ideally, however, commencement of hormone therapy should be delayed until psychiatric assessment has occurred and the diagnosis of the gender dysphoria has been made. All hormone therapy should be monitored clinically and biochemically to allow calculation of the safest dose for the desired effect. The higher doses of oestrogen required for feminization of transsexual males are attended by risks of serious complications, including thromo-embolism, hypertension, stroke, impaired carbohydrate tolerance, gallstones, hyperlipidaemia, and adenomas or prolactinomas of the anterior pituitary gland. Smoking, reduced physical activity and injudicious self-administration of hormones further increase these risks.

Introduction

Transsexuals are usually referred to an endocrinologist for a prescription for hormones, although strictly none of the hormone preparations used for transsexualism has received marketing authority for this purpose. If referred by a psychiatrist it is expected that any psychiatric disorder has been excluded and that the gender dysphoria is not a feature of a personality disorder. However when patients are referred it is important to obtain a full history and confirm the basic gender identity disturbance. The medical history should include past and current medical disorders and a family history of illness especially hypertension and hypercholesterolaemia. The social history is important with regard to behaviour. The person of either sex should be of legal age. If not, a parent or guardian should be involved. A difficulty exists when a young person has rejected their parents because of family attitudes and denies access to them.

A married person poses another problem as medication will affect sexual behaviour and the marriage leading to possible legal action being taken by the spouse against the doctor for interfering with her/his conjugal rights. Hence there should be evidence of separation or a divorce. Unless separation is legally confirmed the spouse may be hoping for reconciliation and think that the dysphoria is a passing phase. The most difficult situation is where both parties wish to remain together in the altered state without a divorce. This should be confirmed by a legal agreement absolving all involved with their treatment. With all precautions this last situation may not be stable. Often the marriage has been an usual relationship arrangement. Female-to-male subjects have walked out of marriages taking children with them. The latter need special care and counselling whether the parent remains in the family or moves away.

The initial interview should explore what the person expects with hormonal conversion/gender reassignment and, in particular, what physical changes they think are likely to occur. The importance of this cannot be underestimated for so often expectations are unrealistic, revealing lack of biological insight. Some transsexuals have expected more than soft tissue change and believed that hormone therapy will alter bone structure and physical stature. When this has not occurred, some have taken their own lives.

Male-to-female conversion

As a group male transsexuals have variable backgrounds.[1] Some have university degrees and professional qualifications while others have not completed secondary school. Before undertaking hormonal conversion it is wise to stress that breast development depends on an adequate number of oestrogen receptors in the target tissue. A trial of hormone administration assesses receptor activity.

The laryngeal prominence does not alter with hormone therapy and, although the timbre of the voice may change slightly, it remains a male voice. Body hair generally responds to treatment but sometimes sparse chest and abdominal hair will remain. Often on first examination the body has been shaved or waxed. Facial hair becomes finer and grows more slowly. At the outset patients should be advised that electrolysis or other depilatory techniques will be eventually unnecessary and that some hair regrowth can be expected after initial treatment.

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Patients must be warned about the risks of deep vein thrombosis with all hormonal medications used especially oestrogens. The latter result in increased blood clotting factors in most people and plasma fibrinogen also rises.[2] This seems more likely with ethinyloestradiol ('Estigyn') than with conjugated oestrogens ('Premarin'), oestradiol valerate ('Progynova') or piperazine oestrone sulphate ('Ogen'). It must be stressed that heavy smoking, inactivity and increasing oestrogen dosage beyond that prescribed increase the risk of thromboembolic disease. However, some patients do not accept this advice and increase dosages by obtaining prescriptions for oestrogen from multiple doctors. Initial examination may reveal gynaecomastia and enlarged nipples indicating previous use of oestrogens that was not admitted in the history. Likewise initial blood assays may show lowered testosterone and pituitary gonadotrophin (LH, FSH) levels indicating prior oestrogen administration. Blood assays before hormone treatment should include testosterone, gonadotrophins, prolactin, dehydroepiandrosterone (DHEAS), and oestradiol as well as a full blood examination, clinical chemistry screens and hepatitis viral serology.

Medications

Oestrogens

Oestrogens can be given orally or parenterally. The most potent oral oestrogen is the synthetic preparation ethinyl oestradiol ('Estigyn') usually given in an amount of 100-300ug daily in divided doses. Unfortunately this drug was withdrawn in July 1997. Alternatively, naturally occurring oestrogens, such as conjugated oestrogens ('Premarin'), can be taken orally in a dose of 0.625mg thrice daily, increasing to 1.25mg thrice daily when required.

Parenteral oestrogen preparations include oestradiol valerate ('Primogyn Depot') for intramuscular injection, skin patches releasing oestradiol ('Estraderm') and subcutaneous implants of oestradiol. 'Primogyn Depot' is usually given in a dose of 2 x 10mg/ml by intramuscular injection every two weeks, while 'Estraderm' skin patches containing 8mg oestradiol (which release 100ug oestradiol over 24 hours) are applied to the skin of the trunk such that 1 new skin patch is applied every three to four days. Oestradiol implants containing 100mg oestradiol are inserted subcutaneously every three to four months. In practical terms both oestradiol implants and 'Estraderm' skin patches are often inadequate in achieving the desired female secondary sexual characteristics.

The feminising effects of oestrogen are first revealed in the breasts which increase in size and become tender. The nipples also increase in size and become more sensitive to touch. With continuing oestrogen therapy, subcutaneous fat is deposited in the typical female distribution – chest, back, buttocks, hips and thighs. This is accompanied by an overall gain in weight. When a transsexual objects to these changes it suggests that they have not really accepted a female body image. Oestrogen also leads to testicular atrophy, reduced penile erectile function and shrinkage of penile tissues. Breast growth and body fat deposition are probably maximal after two years of oestrogen therapy.[3] Blood hormone assays after oestrogen administration reveal a suppression of pituitary gonadotrophins (FSH, LH) and testosterone, while the sex hormone binding globulin (SHBG) and prolactin levels rise.

Untoward effects of oestrogen therapy may occur. Skin pigmentation, particularly if facial, is annoying. Elevated prolactin secretion requires investigation. It may be the result of oestrogen medication but can also be due to a pituitary microadenoma or prolactinoma,[4] requiring treatment with bromocriptine. Ethinyl oestradiol appears less likely to be associated with prolactinoma formation than conjugated oestrogens.[4,5] Gross elevations of blood prolactin levels often associated with galactorrhoea may be accompanied by generalised pituitary enlargement above the fossa, without evidence of a discrete adenoma. In this situation any visual disturbance should be carefully investigated and also there is an increased risk of retinal vascular thrombosis related to changed fibrinogen levels.[2]

The commonest serious complications of oestrogen administration, particularly in the high doses taken by male transsexuals, are deep venous thrombosis and pulmonary embolism, stroke, and hypertension. Therefore, it is essential to take into account a previous history or family history of cardiovascular disease in transsexuals to identify those who require further medical investigation before oestrogen therapy is started. Caution with therapy is also wise in people with hyperlipidaemia, diabetes mellitus and gallstones, as these disorders may be further aggravated by oestrogen. While there is no good evidence to suggest that oestrogen therapy in male transsexuals increases the risk of carcinoma of the breast[6] and prostate,[7] both of these cancers have been reported in these patients. Prostatic obstruction resulting from hypertrophy of the verumontanum has also been reported.[8]

In male transsexuals with androgenic scalp baldness, oestrogen, however administered, is usually ineffective in restoring hair growth. Some patients may have improved hair growth after regular twice daily application of minoxidil lotion to the scalp but the accumulated experience of its use is not encouraging. On the other hand, facial and body hair in transsexual males often becomes less pigmented and finer in response to oestrogen therapy. In those transsexuals, in whom there are medical contraindications to high dose oestrogen therapy, it is appropriate to consider bilateral orchidectomy at an earlier stage than usual in the reassignment procedure. This will reduce testosterone levels into the female range and allow a much smaller dose of oestrogen to be administered to produce the desired result, thereby diminishing the hazards of high oestrogen intake.

Progestogens

While progesterone is not important in inducing feminisation in male transsexuals, it does aid breast growth in some patients and may have a protective effect against both benign and malignant breast disease. Therefore it is theoretically advantageous to prescribe a progestogen to all male transsexuals taking oestrogen. Oral medroxyprogesterone acetate ('Provera') in a dose of 5-

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20mg daily for 14 days continuously in every 28 days is recommended, as it is the least androgenic of the available progestogens. It should be given in addition to the continuously administered oestrogen.

Anti-Androgens

Both cyproterone acetate ('Androcur') and spironolactone ('Aldactone') are used in addition to oestrogen, particularly for male transsexuals who have luxuriant facial and body hair growth. Of these two drugs, cyproterone acetate is regarded as being more effective in suppressing hair growth. However, because of the individual variation in response both drugs are worth a trial in patients in whom one of the drugs used initially has failed to rid them of unwanted hair.

The usual oral dose of cyproterone acetate is 100mg twice daily, whilst that of spironolactone is 200-300mg daily. The former may cause moodiness, and the latter an initial diuresis and weight loss along with a lowering of blood pressure.

Both drugs act on the hair follicle resulting in a slowing of hair growth and a thinning and depigmentation of the hair shaft. These effects are unlikely to be significant under six months treatment.

Female-to-male conversion

Female transsexuals have variable presentations. Some have an androgenic background and have had the polycystic ovary syndrome or congenital adrenal hyperplasia, with elevated blood androgen levels and menstrual irregularities. In contrast, others appear totally normal 'feminine' females until they relate their life history. Masculinization is best achieved by parenteral androgen preparations given intramuscularly, such as testosterone esters in oily solution ('Sustanon') or testosterone enanthate ('Primoteston Depot'). Sub-cutaneous testosterone implants can also be employed but are not favoured by most patients. Oral testosterone undecanoate ('Andriol') in doses of 120-320mg daily has also been used.[9]

In our experience a treatment regimen of 'Sustanon' 100mg intramuscularly every two to three weeks initially, increasing to 250mg every two to three weeks gives the desired response. Within a few months, menstruation usually stops, body hair and facial hair grows, body weight and muscle mass increase, the voice deepens and the female body fat distribution diminishes. Breast size also diminishes somewhat but usually not enough to avoid reduction mammoplasty. The clitoris hypertrophies and may reach the size of a pre-pubertal penis.[3]

Blood hormone assays in female transsexuals taking testosterone reveal a loss of FSH/LH cyclical change, elevated testosterone levels and moderately elevated oestradiol levels. In addition the SHBG decreases, cholesterol may increase, and HDL-lipid falls. Untoward and undesired effects of testosterone therapy include acne, excessive weight gain, hypertension, hypercholesterolaemia, and polycythaemia. Eventually, female transsexuals will require surgical removal of breasts (reduction mammoplasty), hysterectomy and bilateral salpingo-oophorectomy, vaginal ablation and phalloplasty.

Mortality and morbidity

A recent report from Amsterdam indicated that mortality in male-to-female and female-to-male transsexuals taking cross-sex hormone therapy was no higher than in the general population. However, the risk of venous thromboembolism was increased 20-fold in male transsexuals over the age of 40 years while taking oestrogen. For this group the authors recommend transdermal oestradiol as they have obtained some evidence that this mode of administration is associated with a reduced risk of venous thromboembolism. On the other hand no serious morbidity occurred in female-to-male transsexuals receiving androgen therapy.[10]

Conclusion

Hormonal therapy is an essential component of the management of transsexual persons as it is largely responsible for altering physical characteristics so that they become more like those of the desired sex. However, such therapy is not without risks of serious complications and all transsexuals taking hormones should be under adequate medical supervision. This is especially important, when for the true transsexual, hormone administration will be of life-long duration.

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